REMARKS

Claims 1-626 are pending in this application. Of these, claims 1-250, 288-624 and 626 are believed to have been withdrawn from consideration as being drawn to non-elected inventions. Claims 251-285 and 625 are presently under examination. In the claims listing above, claims 251 and 286-287 have each been amended. No claims have been canceled or added by this paper. Accordingly, as reflected in the claim listing above, claims 251-285 and 625 are presented for further examination.

Claim Amendments

As just indicated, claims 286, 287 and 625 have each been amended.[1] Both claims were amended in response to Item No. 2 (Claim Objections) set forth in the November 3, 2006 Office Action.

Claim 625 has also been amended by inserting the term "poly A" before "sequence in said nucleic acid target" in step a)(ii). This term is well supported by Applicants' original disclosure. See, for example, page 20, first three lines:

> . . . In contrast, in the present invention the incorporation of a non-inherent UDT allows a generalized non-specific amplification of nucleic acids comprising the UDT sequences regardless of their particular native sequences. For example, if a library of DNA has a UDT ligated to each end of a series of fragments, the entire library can be amplified. On the other hand, the example above with ***Poly A mRNA and a non-inherent UDT can allow a selective amplification of a generalized population derived from mRNA***. . . . [emphasis added]

[1] In the November 3, 2006 Office Action, claims 286 and 287 are believed to be "withdrawn from consideration" in light of the April 6, 2006 Office Action requiring restriction of invention. To be fully responsive to the present action, Applicants have amended both claims to correct informalities.

Election/Restrictions

Applicants acknowledge that the restriction requirement set forth in the April 6, 2006 Office Action has been made final. It is their intention to file appropriate divisional applications as soon as possible in order to pursue the subject matter of their non-elected inventions.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 251-287 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. According to the November 3, 2006 Office Action (page 3):

> a. Claims 251-287 are vague and indefinite because of the phrase "adding a non-inherent UDT" in the claims. It is unclear whether or not the non-inherent UDT is attached to the extended primers or the extended nucleic acid constructs. Clarification is required.
> b. Claims 269-280 are vague and indefinite because of the phrase "a production center". It is unclear what is the definition of the phrase. Clarification is required.

The indefiniteness rejection is respectfully traversed.

In response, Applicants respectfully point out that the two terms rejected at hand are both amply defined in the predecessor application, U.S. Patent Application Serial No. 09/896,897, filed on June 30, 2001, published as U.S. 2004/0161741 A1 on August 19, 2004. In US 2004/0161741, page 13, these two terms are defined thusly:

> **[0106]** A ***production center*** is a segment of a nucleic acid or analogue thereof that is capable of producing more than one copy of a sequence that is identical or complementary to sequences that are operably linked to the production center.
> **[0107]** ***Universal Detection Targets (UDTs)*** are defined as common or conserved segments in diverse nucleic acids that are present in populations of nucleic acids in a sample and are capable of recognition by a corresponding binding partner. ***The UDTs may be intrinsic or they may be artificially incorporated into nucleic acids.*** Examples of inherent UDTs can comprise but not be limited to 3' poly

> A segments, 5' caps, secondary structures and consensus sequences. Examples of inherent consensus sequences that might find use in the present invention can comprise but not be limited to signal sites for poly A addition, splicing elements and multicopy repeats such as Alu sequences. ***UDTs may also be artificially incorporated into nucleic acids by an addition to the original analyte nucleic acid or during synthesis of nucleic acids that comprise sequences that are identical or complementary to the sequences of the original analytes. Artificially added UDTs may be labeled themselves or they may serve as binding partners.***
>
> [emphasis added]

Later in US 2004/0161741, page 14, "non-inherent UDTs" are further defined as follows"

> **[0113]** This invention also provides a composition of matter that comprises a library of analytes, such analytes being hybridized to an array of nucleic acids, and such nucleic acids being fixed or immobilized to a solid support, wherein the analytes comprise a ***non-inherent universal detection target (UDT)*** and a universal detection element (UDE) hybridized to the UDT, and wherein the UDE generates a signal directly or indirectly to detect the presence or quantity of such analytes. The nature of the analyte, the nucleic acid array, modifications, solid support are as described in the preceding paragraphs above. ***The non-inherent universal detection targets (UDTs) can comprise homopolymeric sequences or heteropolymeric sequences. . . .***

Further on page 19 in US 2004/0161741, "non-inherent UDTs" are described:

> In another aspect of the present invention, ***UDTs or UDEs are artificially incorporated into the diverse nucleic acids of the library***. Enzymes that find particular use with RNA analytes may comprise but not be limited to Poly A polymerase which specifically adds Adenine ribonucleotides to the 3′ end of RNA and RNA ligase which can add an oligonucleotide or polynucleotide to either the 5′ or 3′ end of an RNA analyte. ***By these means, either homopolymeric or unique sequences can be added to serve as UDTs*** or UDEs. Enzymes that find particular use with DNA analytes may comprise but not be limited to Terminal

> Transferase for addition to 3' ends and DNA ligase for addition to either 3' or 5' ends. The sequences that are introduced into the nucleic acid analytes can be labeled during synthesis or addition of a UDE or conversely unlabeled UDTs can be synthesized or added that are detected later by corresponding labeled UDEs. This aspect enjoys special utility when unspliced RNA, snRNA, or rRNA are used as analytes since they may be lacking inherent elements that are present in mRNA that have previously cited as being useful as UDTs. This aspect of the present invention will also find use with procaryotic mRNA since the poly A additions, 5' caps and splicing elements which have been previously cited as potential UDTs of mRNA are intrinsically lacking in procaryotes.

Before closing on the §112, second paragraph rejection, Applicants would like to point out that the non-inherent UDT can be attached either to the extended primers or to the extended nucleic acid constructs. This is clearly seen in the language of original claim 251 ("adding a non-inherent UDT to said extended primers or said extended nucleic acid constructs").

In view of the foregoing, reconsideration and withdrawal of the indefiniteness rejection is respectfully requested.

The Rejection Under 35 USC §102

Claim 625 stands rejected under 35 U.S.C. §102(e) as being anticipated by Laird et al. (6,794,142, Issued on September 21, 2004). According to the November 3, 2006 Office Action (page 3):

> Laird et al. disclose that a primer-based amplification involves repeated primer extensions, wherein at least one of the primers is a modified primer (See column 8, lines *55-57).* The modified primer is at 3' terminus in which the 3' terminal nucleotides are a modified nucleotide, 2'-O-methyl-ribonucleotides (See column 6, lines 50-55). Based upon the teachings set forth above, the teachings of Laird et al. anticipate the limitation of the claim.

The anticipation rejection is respectfully traversed.

As noted above, claim 625 has been amended to recite in step a)(ii) providing at least one primer or nucleic acid construct complementary to a poly A sequence in said nucleic acid target, . . . Thus, claim 625 as amended is distinguishable from the cited Laird patent because the latter does not disclose or suggest amplification of a variety of nucleic acids having a sequence in common (the poly A sequence now recited in the claim). See the specification, page 20, first paragraph (. . . "the example above with Poly A mRNA and a non-inherent UDT can allow a selective amplification of a generalized population derived from mRNA.").

In view of the lack of material identity between the subject matter of claim 625 and Laird et al., Applicants respectfully request reconsideration and withdrawal of the anticipation rejection under §102(e).

The First Rejection Under 35 USC §103

Claims 251-263, 267, 269-285 and 287 stand rejected under 35 U.S.C 5103(a) as being unpatentable over Lin et al. (U.S. Patent No. 6,197,554, issued on March 6, 2001) in view of Laird et al. (U.S. Patent No. 6,4794,142, issued on September 21, 2004). In the November 3, 2007 Office Action (pages 4-6), it is stated:

> Lin et al. disclose a method for generating a complete full-length cDNA library from single cell (See colunm 2, lines 42-44). The method applies a homopolymer dT-promoter primer (See colunm 2, lines *52-55).* The homopolymer dT-promoter primer is complementary to homopolymer dA of m.RNA (See column 2, lines *52-57).* A plurality of cDNAs is produced (See column 2, lines 58-60). The cDNA is tailed by terminal transferase reaction (See column 2, lines 60-64). The full length cDNA library can be made from extracted RNAs by the, same steps from (b) to step f with the difference of total RNAs/mRNAs (See column 5, lines 12-15). Taq polymerase is used in the method (See column 7, line 5). The promoter sequence comprises T3, T7, or SP6 (See colunm 3, lines 28-31). The dNTPs and NTPs are used in the method (See column 6, lines 43-47). The labeling of the eDNA can be accomplished by incorporation of labeled nucleotides or analogs (See

column 5, lines 19-21). The homopolymeric segment is comprised of T (See column 2, lines 54-55) or oligo-C or oligo-G or oligo-A (See column 3, lines 3 1-39).

Lin et al. do not disclose that the primer is modified at 3′ terminal nucleotides with substitution of the 2′ position of the ribose ring, providing the reagent comprising Mn++, the labels recited in claims 278-280 and limitations recited in claims 282-283, 286 and 287.

Laird et al. disclose that a primer based amplification involves repeated primer extensions, wherein at least one of the primers is a modified primer (See colunm 8, lines 55-57). The modified primer is at 3′ terminus In which the 3′ terminal nucleotides are a modified nucleotide, 2′-O-methyl-ribonucleotides (See colunm 6, lines 50-55). DNA polymerase requires Mn++, which is used to increase the efficiency of extension reactions using an RNA template (See column 9, lines 47-53). The mutant Tth DNA polymerases Incorporate dNTPs and ddNTPs labeled with fluorescent (See column 13, lines 12-15). The modified primer is synthesized on a solid support (See column 8, lines 28-35). Laird et al. also disclose that at least one of said nucleotide analogues comprises a portion of said homopolymeric sequence or is different from the base comprising said homopolymeric segment (See column 12, lines 1-49) as recited in claims 286 and 287.

One of ordinary skill in the art would have been motivated to apply a primer which is modified at 3′ terminal comprising nucleotide analogue with substitution on the 2′ position of ribose ring as taught by Laird et al. in the method of Lin et al. for synthesizing one or more copies of a library of nucleic acid targets because as disclosed by Laird et al., the use of oligonucleotide primers containing particular modification at or near the 3′ terminus in a primer-based amplification is to reduce non-specific amplification (See column 3, lines 18-24). It would have been prima facie obvious to apply the primer which is modified at 3′ terminal comprising nucleotide analogue with substitution on the 2′ position of ribose ring for synthesizing one or more copies of a library of nucleic acid targets.

The obviousness rejection is respectfully traversed.

In response, Applicants would like to respectfully point out that the cited Lin patent does not disclose or suggest any problem with non-specific amplification

which the present invention addresses through the use of nucleotide analogs at the 3' end. On the other hand, the cited Laird patent is directed towards increasing the efficiency of amplification of selected specific nucleic acid sequences and it does not disclose or suggest the utility or desirability of its methods for non-selective amplification of a library. Thus, a person of ordinary skill in the art would not have been sufficiently motivated to combine the Lin and Laird disclosures because specificity is not a concern of the former and the latter does not relate to (non-specific) library amplification as set forth in the present claims.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection under 35 U.S.C. §103(a).

The Second Rejection Under 35 USC §103

Claims 264-266 and 268 stand rejected under 35 U.S.C §103(a) as being unpatentable over Lin et al. (6,197,554, issued March 6, 2001) in view of Laird et al. (6,794,142, issued September 21, 2004) as applied to claims 25 1-263, 267, 269-285 and 287 above, and further in view of Austermann et al. (Biochemical Pharmacology, 1992, Vol. 43(12), pg. 2581-2589). As set forth in the Office Action (pages 6-7):

> The teachings of Lin et al. and Laird et al. are set forth in section 8 above. Lin et al. and Laird et al. do not disclose the step of adding a terminator nucleotide as recited in claims 264-266 and 268.
>
> Austermann et al. disclose 3 '-blocked oligonucleotide primers, which inhibit DNA synthesis catalyzed by HIV- 1 reverse transcriptase (See pg. 2581, the Abstract). The oligonucleotide primers were elongated in a terminal transferease-catalysed reaction with dXIATP (See pg. 2581, the Abstract and pg. 2584, column 1, third paragraph). The terminator is ddATP, or arabino-ATP (See pg. 2586, Table 3).
>
> One of ordinary skill in the art would have been motivated to apply the 3'-blocked oligonucleotide primer as taught by Austermann et al. because the 3'-blocked oligonucleotide primer act as strong

inhibitor of DNA synthesis catalyzed by HIV-1 reverse transcriptase (See pg. 2581, the Abstract). It would have been prima facie obvious to have a step of adding a terminator nucleotide by providing terminal dioxynucleotidyl transferase and a mixture of terminator and non-terminator for synthesizing one or more copies of a library of nucleic acid targets.

The second obviousness rejection is respectfully traversed.

At the outset, Applicants incorporate by reference their remarks above with respect to the Lin and Laird patents. With respect to claim 264, the addition reagents comprising terminal deoxynucleotide transferase or a ligase are used to provide the non-inherent UDT in step d) of claim 251. In contrast, Austermann et al. describe the use of 3' blocked oligos for HIV antisense inhibition, and such oligos could and would not be used in step d) of claim 264.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the second obviousness rejection.

Favorable action on this application is respectfully requested.

* * * * * * *

SUMMARY AND CONCLUSIONS

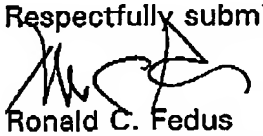
A complete listing of the claims in this application are provided above. In the complete listing of the claims, 286, 287 and 625 have been amended.

No fee or fees are believed due for this paper, apart from the Request For Extension Of Time (3 Months) and authorization for the small entity fee therefor. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Early and favorable action is respectfully requested.

Respectfully submitted,



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